Remarks

Claims 1, 3, 4, 6, 19, 20, 26 and 27 are currently pending. Claims 1, 3, 4, 19, 20, 26 and 27 are currently amended. Claims 2 and 5 are cancelled. Claims 7, 18 and 21 – 25 are withdrawn. Support for the amendments to the claims can be found at, for example, paragraphs [0045], [0046], [0047] and the sequence listing.

The Applicant enclosed a certified copy of French Patent Application No. 01/07805 filed June 14, 2001.

Claims 3, 4, 6, 26 and 27 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection alleges these claims are indefinite because they recite "capable of hybridizing under strict conditions[.]" Claims 3, 4, 26 and 27 have been amended to remove to the language "capable of hybridizing under strict conditions[.]" Claim 6 depends on amended Claim 4 and incorporates all of its recitations. The amendments to Claims 3, 4, 26 and 27 render the rejection under 35 U.S.C. §112, second paragraph, of these claims as being "indefinite" moot. The Applicant respectfully requests withdrawal of the rejections of claims 3, 4, 6, 26 and 27 under 35 U.S.C. §112, second paragraph.

Claims 1 and 3 are rejected under 35 U.S.C. §102(b) as being anticipated by Surmacz. The rejection alleges that Surmacz teaches an antisense oligonucleotide that comprises at least 12 nucleotides that bind SEQ ID NO: 28 at the twenty (20) nucleotides down stream of the start codon.

Surmacz is not an anticipating reference under 35 U.S.C. §102(b). Surmacz only discloses a single antisense oligonucleotide of sequence 5'-cgctcgggaggcctatggct-3' that was "designed to hybridize with the 20 bases following the...["aug"] codon in the mouse IRS-1 mRNA[.]" *See* Surmacz at 1430. The antisense oligonucleotide disclosed in Surmacz is not

identical to the antisense strand sequence complementary to the twenty (20) base pairs following the "atg" start codon in residues 1022 – 4747 of SEQ ID NO: 28 as shown in Table 1.

Table 1.

Part A)   Antisense/noncoding strand complementary to the twenty (20) bases following the "atg" stop codon (bold text) at position 1022 on the sense/coding strand of SEQ ID NO: 28.

SEQ ID NO: 28 Sense/Coding Strand Residue 1022 5'-atggcgagccctccggagagcga-3' 1044 etc.
SEQ ID NO: 28 Antisense/Noncoding Strand   3'-taccgctcgggaggcctctcgct-5'

Part B)   Comparison of the Surmacz antisense oligonucleotide to the corresponding antisense/noncoding strand region of SEQ ID NO: 28.   (bold, underlined text highlights non-identical residues)

SEQ ID NO: 28 Anti-Sense/Non-Coding Strand   5'-**tcgctctccggagggctcgccat**-3'
Surmacz   Antisense Oligonucleotide   5'-**cgctcgggaggcctatggct**----3'

As shown in Table 1, the antisense oligonucleotide described in Surmacz would not be capable of hybridizing to the corresponding antisense/noncoding strand region of SEQ ID NO: 28, because it has only two nucleic acid residues that are identical to this region of the antisense/noncoding strand of SEQ ID NO: 28. In fact, BLASTN analysis using the default settings and settings adjusted for short nucleic acid sequences (Word Size = 7; Expect Value = 1000; Filtering = Off) show that the antisense oligonucleotide taught in Surmacz appears to have no significant identity to any portion of the antisense/noncoding strand complementary to SEQ ID NO: 28. In light of the foregoing, Surmacz does not describe an antisense oligonucleotide within the scope of claims 1 and 3. The Applicant respectfully requests the withdrawal of the rejections of Claims 1 and 3 over Surmacz under 35 U.S.C. §102(b).

Claim 19 is rejected under 35 U.S.C. §102(b) as being anticipated by Wolf. The rejection states that Wolf discloses double-stranded human IRS-1 cDNAs in vectors and that these vectors would comprise the SEQ ID NO:s recited in the claims.

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Claim 19 is not anticipated under 35 U.S.C. §102(b) by Wolf. Claim 19 has been amended to recite "isolated antisense nucleic acid molecule[s] consisting essentially of a nucleotide sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22 and SEQ ID NO. 23." Wolf does not anticipate amended Claim 19, because it does not teach antisense nucleic acid molecules, does not enable one of ordinary skill in the art to make such antisense molecules and provides no teachings concerning antisense molecules. Further, Wolf does not teach small antisense nucleic acid molecules "consisting essentially of" those described by SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22 and SEQ ID NO. 23. In light of the foregoing, it is clear that Wolf does not qualify as a 35 U.S.C. §102(b) reference against amended Claim 19, because it does not enable one of ordinary skill in the art to make the claimed antisense molecules, and does not teach antisense nucleic acid molecules consisting essentially of those described by the SEQ ID NO:s of Claim 19. The Applicant respectfully requests the withdrawal of the rejection of Claim 19 under 35 U.S.C. §102(b) over Wolf.

Claims 1, 3 and 6 are rejected under 35 U.S.C. §103(a) as obvious over the combination of Surmacz, Nolan and Bennett. The rejection states that Surmacz discloses "an antisense oligonucleotide that comprises at least 12 nucleotides that bind to SEQ ID NO: 28 at the 20 nucleotides down stream of the ["atg"] start codon[.]" This "atg" start codon is located in the

sense/coding sequence shown in residues 1022 – 4747 shown in SEQ ID NO: 28. *See* Table 1.

The rejection asserts that Nolan discloses the inhibition of mouse IRS-1 protein expression with full-length antisense constructs. The rejection states that Bennett teaches pharmaceutically acceptable carriers that can be used to enhance antisense uptake and be used for *in vivo* applications. The rejection thus relies on establishing *prima facie* obviousness, instead of an alternative rationale supporting the conclusion of obviousness.

Claims 1, 3 and 6 are not obvious under 35 U.S.C. §103(a) over the combination of Surmacz, Nolan and Bennett. Surmacz does not describe an antisense oligonucleotide that "would inhibit expression of a peptide chain encoded by nucleic acid residues 1022 – 4747 shown in SEQ ID NO: 28" as discussed above. Nolan teaches antisense constructs comprising the entire sequence of the mouse IRS-1 antisense/noncoding strand, but BLASTN analysis shows that the most identical mouse (*Mus musculus*) homolog of the cDNA encoded by SEQ ID NO: 28 has only 85% identity to the protein coding open reading frame encoded by residues 1022-4747 shown in SEQ ID NO: 28. This means Nolan does not describe an antisense oligonucleotide that "would inhibit expression of a peptide chain encoded by nucleic acid residues 1022 – 4747 shown in SEQ ID NO: 28[.]" Together, neither Surmacz or Nolan teach active agent "molecule[s] comprising a nucleic acid which inhibits expression of a peptide chain encoded by nucleic acid residues 1022 – 4747 shown in SEQ ID NO: 28 [or] a fragment of said molecule comprising at least 12 continuous nucleotides which inhibits expression of a peptide chain encoded by nucleic acid residues 1022 – 4747 shown in SEQ ID NO: 28." Bennett similarly fails to disclose such active agent molecules. Consequently, the combination of Surmacz, Nolan and Bennett fails to teach all of the elements of amended Claims 1, 3 and 6 and fails to establish *prima facie* obviousness. The Applicant respectfully requests withdrawal of the

rejections of claims 1, 3 and 6 under 35 U.S.C. §103(a) over the combination of Surmacz, Nolan and Bennett.

Claims 19 and 20 are rejected under §35 U.S.C. 103(a) as being obvious over the combination of Surmacz, Nolan, Bennett and Wolf. The rejection states that the teachings of Surmacz, Nolan and Bennett are as discussed above. In particular, the rejection states that Surmacz teaches "the human and mouse [protein] sequences of IRS-1 are 90% identical." (Emphasis added; please note Surmacz teaches at page 1433 ">90% homology" not identity). The rejection also states that "the vectors used by Nolan" contain the mouse antisense sequence. The rejection then states that Wolf discloses that the sequence of human IRS-1 was known and that it would be "obvious to use a human IRS[-1] sequence expressed in the antisense orientation" as taught for the mouse antisense constructs described in Nolan. This rejection also relies on establishing *prima facie* obviousness, instead of an alternative rationale supporting the conclusion of obviousness.

The rejection fails to establish *prima facie* obviousness over the combination of Surmacz, Nolan, Bennett, and Wolf. The combination of Surmacz, Nolan and Bennett fails to teach all of the elements of the claims 19 and 20 for essentially the same reasons as discussed above. Nolan does, however, teach full-length antisense constructs corresponding to the complimentary strand of the cDNA encoding mouse IRS-1. The rejection asserts that Wolf teaches the human sequence of IRS-1 and that one of ordinary skill in the art would be able to make the type of full-length antisense construct described in Nolan. Claim 19 has been amended to recite "[a]n isolated antisense nucleic acid molecule consisting essentially of a nucleotide sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ

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ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22 and SEQ ID NO. 23." Claim 20 is dependent on Claim 19 and incorporates all of its recitations. The combination of Surmacz, Nolan, Bennett and Wolf would not result in the antisense nucleic acid molecules consisting essentially of the SEQ ID NO:s listed above. This is because combining the teachings of Nolan, Wolf, and the other cited references would only produce a human antisense construct comprising a full-length nucleic acid sequence complimentary to the full-length cDNA encoding human IRS-1, not smaller fragments of the nucleic acid cDNA encoding the human IRS-1 protein sequence. Consequently, it is clear that the combination of Surmacz, Nolan, Bennett and Wolf would not produce the claimed antisense molecules as these references do not teach the elements of the claimed inventions and thus fail to establish *prima facie* obviousness. The Applicant respectfully requests withdrawal of the rejections of claims 19 and 20 under 35 U.S.C. §103(a) over the combination of Surmacz, Nolan, Bennett and Wolf.

In light of the foregoing, the Applicant respectfully submits that the entire Application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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